CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

CAPTAFOL

SB 950-009, Tolerance # 267

July 28, 1986
Revised November 14, 1986
Revised February 27, 1987
Revised April 28, 1987
Revised January 11, 1989

I. DATA GAP STATUS

Combined (chronic + onco) rat: No data gap, possible adverse effect.

Chronic dog: No data gap, no adverse effect.

Onco mouse: No data gap, possible adverse effect.

Repro rat: No data gap, no adverse effect.

Terato rat: No data gap, no adverse effect.

Terato rabbit: No data gap, no adverse effect.

Gene mutation: No data gap, possible adverse effect.

Chromosome: No data gap, no adverse effect.

DNA damage: Data gap, inadequate study.

Neurotox: Not required at this time.

----------**Note, Toxicology one-liners are attached**

** indicates acceptable study
Bold face indicates possible adverse effect
File name T890111, revised January 11, 1989 by J. Gee

II. TOXICOLOGY SUMMARY

COMBINED (CHRONIC + ONCO), RAT

** **032-4 946395-7** "Chronic Toxicity Study in Rats; Difolatan, Final Report." (6/15/1983, Hazleton, # 2107-103) Acceptable with adverse effects noted in chronic toxicity, ulcerated areas in the stomach in high dose, renal tubule cell carcinoma, increased mammary fibroadenomas in females, increased hepatic neoplasms in females. Fifty per sex/group were fed 75, 300 or 1200 ppm for 122-123 weeks. Systemic NOEL = 75 ppm. J. Wong, 2/28/85.
EPA 1-liner: Oncogenic NOEL = 300 ppm (fibroadenomas of female mammary glands), Systemic NOEL = 75 ppm (omission of discolored livers in males and fibroadenomas of female mammary gland); SUPPLEMENTARY.

061 28494 Addendum to 946395 - histopathology. JR, 9/10/85.

051-3 014213-5 "Single Dose Level Chronic Oral Toxicity and Oncogenicity Study in Rats; Difolatan; Final Report." (10/4/1984, Hazleton, Project 2107-108) Unacceptable - single dose only but a "satellite" study to 946395-7 (see above). Fifty per sex per group were fed 0 or 85 ppm. This is slightly higher than the 75 ppm in the other study. No significant adverse effect is reported. J. Wong, 3/4/85.
EPA 1-liner: Oncogenic NOEL≥ 85 ppm (only dose tested); Core grade SUPPLEMENTARY.

CHRONIC, RAT

008 30930 (formerly 946392) Same study as 946393, with raw and tabulated data. More complete version. Non-validated IBT study, 1964.

015 30930 (formerly 946393) Partial duplicate of 946392. JW, 2/28/85.

CHRONIC, DOG

008 030929 (formerly 946400) More complete version of study 946394, with additional raw data.

015 030929 (formerly 946394) Summary narrative only. Non-validated IBT study. J. Wong, 2/28/85.

103 50281 Stability data for captafol. Addendum to 39860.

** 039860 "One-Year Subchronic [sic] Oral Toxicity Study in Dogs." (9/17/85, Hazleton, VA, No. 2107-111) Chronic, 1-year study in dogs given captafol, 98%, in gelatin capsules at doses of 0, 2, 40 or 250 mg/kg/day, 6/sex/group. At 250 mg/kg/day, emesis postdose, soft feces, slight reduction in serum albumin and phosphorus were noted along with increased kidney weight associated with decreased body weight in high dose females with the NOEL at 40 mg/kg/day. Reviewed as acceptable by F. M., 4/14/86 and J. G., 1/18/87 with submission of 103-050281 for stability data. During health effect assessment, an additional effect on the kidney and urinary bladder of females was noted which appeared to be treatment related, notably "ballooning/vacuolar degeneration" of the epithelium at incidences for kidney of 0/6, 2/6, 3/6 and 4/6 and for urinary bladder, 0/5, 2/6, 3/6 and 3/6. No comparable finding in males. The NOEL for these effects is < 2 mg/kg/day in females with the biological significance unclear. No clear adverse effect. Gee, 1/11/89.

ONCOGENICITY, MOUSE

** **020 946403** "Lifetime Oncogenic Feeding Study of Difolatan Technical (SX-945) in CD-1 (ICR Derived) Mice." (6/28/1982, Chevron # 1330) Acceptable with positive adverse effects noted in the stomach, non-neoplastic lesions in pancreas, kidneys. Oncogenicity: hemangiosarcoma, lymphosarcoma. 104 combined controls from two concurrent studies and 80/sex/group were fed 300, 1000 or 3000 ppm. J. Wong, 3/6/85.
EPA 1-liner: Oncogenic NOEL = 300 ppm (lymphosarcomas, myeloproliferative disease); Systemic NOEL = 300 ppm (decreased body weight, increased mortality, decreased hematological parameters, atrophy of pancreas, testicles, spleen, bone marrow and kidney tissue); Core grade: SUPPLEMENTARY.

021-027 946404-10 Addenda to 946403. Detailed histopathology. JRG, rereview; conclusions are the same.

050 14211 Addendum to 946403 3/21/84 revision of main text of 946403. Reviewed by JW.

055 27081 Addendum to 946403. Reevaluation of myeloproliferative disease.

061 28495 Addendum to 946403 Separate control pathology data.

016 946402 Partial duplicate of 946403.

093 47034, 47035 "Carcinogenicity of Captafol in B6C3F1 Mice." (10/84, Nagoya City University Medical School), publ. in Gann 75: 853-865 (1984). B6C3F1 mice were fed 0, 0.075, 0.15 or 0.3% Captafol (94.9% purity) in the diet; 50 or 51/sex/group; dose selection based on a 13-week study; high dose group had no survivors in either sex at termination of study (2 years); positive carcinogenic effect reported - hemangioendotheliomas in heart, neoplasms in forestomach and small intestine, hepatic and splenic tumors; Also, non-neoplastic chronic nephropathies were noted in both sexes at the high dose. 47035 is a Data Evaluation Report from the Tox. Branch on the publication with the classification of "core-supplementary." J. Gee, 9/18/86.

REPRODUCTION, RAT

009 946428 (1965, IBT #B2804) = invalid IBT study

017/028 946430 Progress report (11/82, Biodynamics #80-2530) JW 2/25/85 See 37781-6.

041 14749 (1983, Biodynamics #80-2530) JW, 2/27/85. Evaluated as unacceptable due to insufficient information (only 1 of 5 volumes presented). 37781-86 is complete report. J. Gee, 3/26/86.

** 072-7 037781-6 "A Two-generation Reproduction Study in Rats with Difolatan." (10/10/1983, Biodynamics, Project No. 80-2530) Complete, acceptable. No adverse reproductive effect. Captafol (98-99% purity) was fed in diet at 0, 85, 300, and 1200 ppm over 2 generations, 2 litters in the second generation. 12 males/24 females per group. NOEL: 300 ppm (parental toxicity.) Because of the total number of litters, the lower number of males was judged acceptable. J. Gee, 3/26/86.
EPA 1-liner: Reproductive NOEL > 1200 ppm (HDT) Maternal NOEL= 259 ppm based on actual content - see vol. 077 Core grade: SUPPLEMENTARY 003114 MINIMUM 0039216

TERATOLOGY, RAT

** 095 48857 "Teratology Study in Rats with Chevron Captafol Technical." (Argus Labs, 7/25/86) Captafol, tech. (97%). 0, 4, 30, and 200 mg/kg/day by gavage in aqueous suspension (with Tween 80 and sodium CMC). Maternal NOEL = developmental toxicity NOEL = 30 mg/kg/day (Maternal effects: mortality (2 deaths), rales, chromodacryorrhea, labored breathing, GI disturbances, marked decrease in weight gain, etc. Fetal effects: Decreased fetal weights, slight decrease in ossification (seen in phalanges.) No significant adverse developmental effects. Complete and ACCEPTABLE report. C. Aldous, 11/7/86.

005 946416 (1967, IBT) #5397 = invalid IBT study

047 14746-7 (1983, Biodynamics) Identicalto 37780.

071 37780 "A Teratology Study in Rats with Captafol Technical." (10/14/1983, Biodynamics, Project No. 83-2716) Captafol (97.6% purity); 25/group were given 0, 4, 20 and 100 mg/kg/day on days 6-19 by oral gavage; NOEL: 20 mg/kg/day on maternal body weight (at 100 mg/kg/day, maternal weight was lower by 3-4%). NO teratogenic effect is reported. The study is unacceptable primarily on the basis of dose selection in that the high dose was marginal in toxicity. A pilot study at 180 mg/kg gave a marginal weight effect and the dose selection must be justified by the sponsor. The pregnancy rate was 17-20/25 possibly due to a sialodacryoadenitis viral infection and the report states the effect on pregnancy in rats is not known. Unacceptable but upgradeable (justification of dose selection.) J. Gee, 3/25/86.
EPA 1-liner: Terat. fet. mat. NOEL > 100 mg/kg/day (HDT) Core grade: MINIMUM.

TERATOLOGY, RABBIT

004 946417 (1967, IBT) #J5061 = invalid IBT study.

017/036 946419 Summary of pilot study for 946420.

030 946423 Pilot study to 946420

** **017/031 946420** (10/14/1982, Bio-Research #81154) JW, 2/25/85. New Zealand strain, 16/group were given 5, 16.5 or 50 mg/kg/day by gavage on days 6-28 of pregnancy. At the high dose, 27% maternal mortality was observed. Positive adverse effects were noted by JW in the initial review especially at the high dose in the presence of maternal toxicity. This study should be rereviewed in view of 37779 below. The effects noted were increased resorptions and

post-implantation loss, retarded ossification at 16.5 and 50, sternebral anomalies at 16.5 and 50. NOEL: 5 mg/kg/day. [Initial Tox Summary had a NOEL of 50 mg/kg - a typographical error.] Acceptable.
EPA 1-liner, based on draft report 10/14/82: Teratogenic, fetotoxic, NOEL = 5 mg/kg/day (exencephaly and hydrocephaly; skeletal anomalies, decreased fetal body weights; Maternal NOEL < 5 mg/kg/day (decreased body weight gain). Core grade: SUPPLEMENTARY.

042 039971 "Teratology Study in the Rabbit." (12/6/1983, Bioresearch Project No. 81154) Final draft of 946420. Exact duplicate with the addition of sign-off sheet signatures. See 946420.
EPA 1-liner based on Final report 12-6-83: Teratogenic NOEL > 50/mg/kg/day (HDT). Fetotoxic, maternal NOEL = 16.5 mg/kg/day (increased minor skeletal abnorm. and resorptions.) Core grade: MINIMUM.

047 14745 (12/1983, Bioresearch #81154) Duplicate of 39971.

047 14743-4 (1984, Biodynamics #83-2734) Partial duplicate of #37779.

** 070 037779 "A Teratology Study in Rabbits with Captafol Technical: Final Report." (2/22/1984, Bio/dynamics, No. 83-2734) Complete, acceptable. Captafol (98% purity) was given at 0, 4, 16 and 50 mg/kg/day by oral gavage to 17/group, New Zealand strain; NOEL (fetotoxicity): 16 mg/kg/day; NOEL (maternal toxicity): 4 mg/kg/day. NO teratogenic effect is reported. J. Gee, 3/24/86.
EPA 1-liner: Teratogenic NOEL > 50 mg/kg/day Fetotoxic NOEL = 16 mg/kg/day
Maternal NOEL = 4 mg/kg/day Core grade: MINIMUM

Summary (4/29/87): The rabbit teratology studies were reexamined in order to resolve the discrepancy between the results of the two studies. The first study (Record # 946420) indicated a maternal NOEL of 16.5 mg/kg/day and a developmental NOEL of 5 mg/kg/day while the repeat study (Record # 37779) indicated a maternal NOEL of 4 mg/kg/day and a developmental NOEL of 16 mg/kg/day. In the first study, there were malformations in two litters (four

fetuses) at 16.5 mg/kg (mid dose) and in two litters (two fetuses) at 50 mg/kg/day (high dose). The malformations were different in the two dose groups, the incidence was not statistically significant relative to controls and the incidence did not increase from the mid to the high dose group. Minor skeletal anomalies were found in all groups. In some cases, when examined on a fetal basis, specific skeletal anomalies were elevated relative to controls but not in a dose-related manner. The total incidence of minor skeletal variations in the high dose group, when examined on a fetal basis, was significantly elevated above controls. There was no difference from controls when the incidence was evaluated on a litter basis. The incidence of resorptions was higher than control in the treated groups but only significant in the high dose group. Mean fetal body weights were slightly, but not significantly, decreased in the treated groups. The study was confounded by a bacterial respiratory infection in all groups, which complicates the interpretation of many of the effects. In this first study, the evidence was not convincing that developmental toxicity occurred at dose levels that were not also maternally toxic. The repeat rabbit teratology study showed developmental toxicity only at dosages that exceeded the maternally toxic level. In this study, the fetuses and dams were examined in great detail and the study was not complicated by concurrent disease. The weight of evidence clearly indicates that captafol is not a developmental toxin in the rabbit. J. Schreider, 4/28/87.

TERATOLOGY, MONKEY

003 946421 (1968, Bionetics) JW, 2/26/85. Unacceptable - no guidelines for studies in this species. No teratogenic effect reported. Seven monkeys per group were given 6.25, 12.5 or 25.0 mg/kg by gastric intubation daily days 22-32. Thalidomide was the positive control.

036 946426 (1968, IBT) JW, 2/26/85. See 946421. Part of study was done by IBT. Invalid.

MUTAGENICITY, GNMU

Microbial systems

050 014212 (1982, Chevron) JW, 2/26/85 & JR, 3/24/86.
Unacceptable with information supplemental only. Salmonella strain TA 100; tested at 0, 0.001, 0.01, 0.1, 0.5 and 1.0 ug/plate. Mutagenic activity was seen with activation at 0.1 and 0.5 and a positive adverse effect noted by JW. Since only one strain was used and a single trial, no evaluation of significance can be made. In 37790 (see below) using a different strain, mutagenicity was also reported.

081 037790 "Microbial/Mammalian Microsome Mutagenicity Plate Incorporation Assay: Comparison of Captan Technical (SX-1086), Chevron Folpet Technical (SX-1388) and Chevron Captafol Technical (SX-945)." (2/8/1984, Chevron) Salmonella strain TA102 only. Captafol, 97.6%, at 1 ug/plate without activation only, plus cysteine and glutathione in increasing concentrations. Increase in revertants without either of these added was approximately 4 fold. Unacceptable with positive mutagenic effects. J. Gee, 3/24/86.

090 043502 "Microbial/Mammalian Microsome Mutagenicity Plate Incorporation Assay with Difolatan (Captafol Technical, SX-945)." (1/8/1986, Chevron). Salmonella, E. coli. Strains TA98, TA100 and TA102 for Salmonella and WP2 uvrA for E. coli. With and without rat liver activation; triplicate plates, repeat trial; positive mutagenic effect +/- S9 in TA 102 and E. coli; 0, 0.001, 0.003, 0.001, 0.003, 0.01 or 0.03 mg/plate in plate incorporation assay; unacceptable study, incomplete (purity and lot number used need confirmation and the statement that report is "Excerpted from SOCAL 2292 and SOCAL 2412" needs explanation). Upgradeable. J. Gee, 9/18/86.

Mammalian systems

084 039857 "Evaluation of Chevron Captafol Technical in the Mouse Somatic Cell Mutation Assay." (6/1985, Litton Bionetics) Mouse spot test. Unacceptable study using a protocol not listed in FIFRA. Captafol, 97%, was fed in the diet to female mice (F1 cross of T-strain males and C57Bl/6 females) at 100, 400 or 1700 ppm, days 8.5 through 12.5 of gestation. Fetuses were monitored for color changes due to mutation of melanocytes. NO evidence of a mutagenic effect was reported. The study resembles a teratology study more than a mutagenic study and is judged as a no test. J. Gee, 4/14/86.

** **091 045031** "CHO/HGPRT Mammalian Cell Forward Gene Mutation Assay. (1986, Pharmakon, PH-314-CH-001-85). CHO/HGPRT with and without rat liver activation at 0 to 30 ug/ml, duplicate cultures, repeat trials; positive mutagenic effect at several concentrations without S9; no mutagenicity with S9; acceptable. J. Gee, 9/18/86.

MUTAGENICITY, CHROMOSOMES

012/001/029 946427 "Dominant Lethal Study of Difolatan Technical." (1/3/1980, Chevron) Unacceptable with no adverse effect. Initial review by JW noted possible adverse effects. Difolatan technical, 97.3%; Rats, 20 males per group, were given 50, 100 and 200 mg/kg by intragastric route and mated for five consecutive days over a series of weeks. A decrease in viable fetuses and implants was noted in the 5th week. Because no individual data are included, the significance is difficult to evaluate. Since there is an effect in a single week well into the mating schedule, the finding is of doubtful significance. Although initially evaluated as acceptable (JW), reevaluation changes this based on the lack of all individual data. J. Wong, 2/25/85 and J. Gee, 3/4/86.
EPA 1-liner: ACCEPTABLE - Negative up to 200 mg/kg/day (highest level tested.)

041 014750 (1983, E.G. & G. Mason.) JW 2/28/85, JRG 3/4/86 Unacceptable with insufficient information. In vivo cytogenetics in rats. See 37787 below for more complete report.

** 078 037787 "In Vivo Cytogenetics Study in Rats - Captafol Technical (SX-945)." (9/7/1983, E.G. & G. Mason, MRI 224-cc83-31) Captafol, 98%, was given to 4 rats/sex/group at 0, 85, 265, 1000 and 1500 mg/kg by gavage. Rats were sacrificed at 6, 24 and 48 hours and 50 cells per animal were examined for chromosomal aberrations. Acceptable with no adverse effect reported. J. Gee, 3/4/86.
EPA 1-liner: ACCEPTABLE - No chromosome aberrations HID = 1500 ug/kg
[sic, should read 1500 mg/kg, the highest concentration used]

050 014210 "Pilot Inhalation Toxicology and Cytogenetics Study in the Rat and Guinea Pig: Technical Difolatan: Final Report." (Litton Bionetics, 10/82, Project No. 22150-01/11) Difolatan, 99.5%; target exposures were 0, 1, 10 or 100 mg/m^3; all data on cytogenetics portion (Appendix 6) are missing. Cannot evaluate for cytogenetic effect. J. Gee, 2/19/87.

MUTAGENICITY, DNA/OTHER

058 028404 "Inhibition of Testicular DNA Synthesis by Chemical Mutagens and Carcinogens. Preliminary Results in the Validation of a Novel Short Term Test." (Swiss Federal Res., 1977, publication in Mutation Research 46: 305-310 (1977), J. P. Seiler) Captafol, no purity stated, given p.o. at 500 mg/kg to male mice, 3-4 animals; incorporation of [^{3}H]-thymidine into testicular DNA measured per ug DNA; sacrifice time not stated; captafol reported at 97.6% of control; negative for adverse effect. Unacceptable due to insufficient information. J. Gee, 2/19/87.

MUTAGENICITY, GENERAL

039 014755 "Summary of Results of Mutagenicity Testing of Captafol Technical (Difolatan)." (Chevron, 1983) Brief review of published and unpublished reports on in

vitro and *in vivo* genotoxicity tests. Table I lists the *in vitro* and Table II is missing. Positive effects were seen *in vitro*; *in vivo* tests tended to be negative, suggesting detoxification in animals. List of references. J. Gee, 2/19/87.

NEUROTOXICITY

Not required at this time.

Other mutagenicity studies have been identified in the EPA 1-liner files.

842/844
Mutation Research *40* 19-30 1976. Screening of pesticides. Captafol identified as mutagenic.
EPA 1-Liner: Reverse mutations induced in *E. coli* wp2 hcr^+ and hcr^- DNA damage induced in the *B. subtilis* H17/M45 system. ACCEPTABLE.

843
Mutation Research *78* 177-191 1980. Sister chromatid exchange and chromosomal aberrations in CHO cells in culture.
EPA 1-Liner: Positive . LEL for chromosome aberrations = 1.0×10^{-5} LEL for SCE's = 5.0×10^{-6} M; ACCEPTABLE

842
Mutation Research *57* 259-263 1978. Effects of cysteine and a liver metabolic system on the activities of mutagenic pesticides.

EPA 1-Liner: Preincubation of folpet with S-9 mixture, S-9 fraction rat blood, or cysteine greatly reduced or eliminated the ability of captafol to induce reverse mutations in E. coli wp2 hcr and S. typhimurium TA1535. ACCEPTABLE.